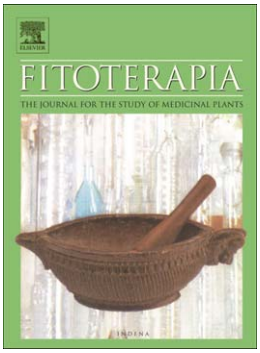

Diversity, pharmacology and synthesis of bergenin and its derivatives: Potential materials for therapeutic usages

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Review

Diversity, pharmacology and synthesis of bergenin and its derivatives: Potential materials for therapeutic usages

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Abstract
Bergenin, a natural secondary metabolite, has been isolated from different parts of a number of plants. It is one of active ingredients in herbal and Ayurvedic formulations. It exhibits antiviral, antifungal, antitussive, antiplasmodial, antiinflammatory, antihepatotoxic, antiarrhythmic, antitumor, antiulcerogenic, antidiabetic and wound healing properties. It has been analyzed and estimated in different plant extracts, blood and drug samples using chromatographic techniques, and pharmacokinetic studies have been made. Several bergenin derivatives were isolated and/or synthesized and were found to possess pharmacological activities. Total synthesis of bergenin and its derivatives were reported. This review article covers literature on bergenin and its derivatives until 2013. Ethnomedicinal value of bergenin containing plant materials is also highlighted. This comprehensive review provides information on the potentiality of bergenin and its derivatives for therapeutic usages.

***Keywords*:** Analytical technique; Bergenin; Natural occurrence; Pharmacological activity; Synthesis

Contents

Abbreviations: ABTS, 2,2'-azinobis-3-ethylbenzotiazoline-6-sulfonic acid; DCC, dicyclohexylcabodiimide; DEAD, diethyl azodicarboxylate; DIAD, diisopropyl azodicarboxylate; DMAP, N,N-dimethylamino pyridine; DME, 1,2-dimethoxyethane; DMF, N,N-dimethylformamide; DPPH, 2,2-diphenyl-1-picrylhydrazyl; EDC, ethyldimethylaminopropylcarbodiimide; IFN, interferon; IL, interleukin; MIC, minimum inhibitory concentration; PPTS, pyridinium p-toluenesulfonate; TBAF, tetra-n-butylammonium fluoride; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy free radical; Th, helper T cell; THF, tetrahydrofuran; TNF, tumor necrosis factor.

1. Introduction of bergenin

Natural polyphenols of plant origin are often associated with medicinal values and are often used as intermediates for industrial products and pharmacological applications. Recent studies have proved that bergenin (**1**) (Fig. 1) possesses good pharmacological properties with low side effects and little toxicity. As indicated from the result of the ^{14}C-glucose incorporation experiment in *Saxifraga stolonifera* leaves, gallic acid is considered as the glucosyl acceptor for the biosynthesis of bergenin in nature [1]. Under continuous light, bergenin present in the young leaves showed the highest incorporation of label from ^{14}C-glucose and the addition of unlabeled gallic acid enhanced the incorporation label.

Bergenin (**1**) (also known as ardisic acid B, bergenit, bergenitol, cuscutin, peltophorin and vakerin) is a C-glucoside of 4-O-methyl gallic acid (2β-D-glucopyranosyl 4-O-methyl gallic acid δ lactone). It is an isocoumarin, hydrolysable tannin that obtain as a colorless crystal from MeOH. It has poor solubility in water, easily degrades in basic solution and its stability mostly depends on the storage conditions [2]. The initial structures of bergenin given by Tschitschibabin et al. (structure **I**) in 1928 [3] and Shimokôriyama (structure **II**) in 1950 [4] were revised by Hay et al. [5], Posternak et al. [6] and Fujise et al. [7] (Fig. 1). The structure of bergenin (**1**) was unequivocally confirmed through X-ray analysis of its 3,4,8,10,11-penta acetate derivative [8] and monohydrate [9,10].

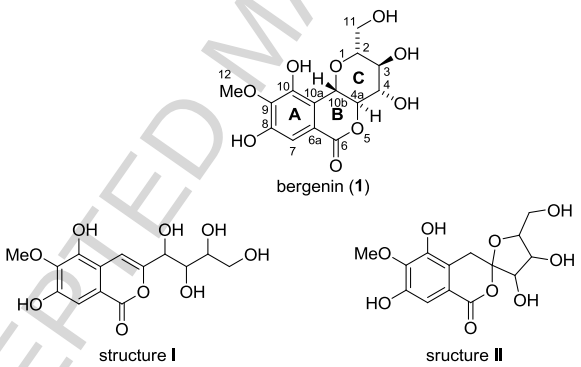


Fig. 1. Structure of bergenin.

2. Occurrence of bergenin in nature

According to citation in the Merck Index, bergenin (**1**) was first isolated from the rhizomes of *Saxifraga* (*Bergenia*) *siberica* [11]. Later, the compound was isolated from a number of plant sources (Table 1).

Table 1
List of plants used for the isolation of bergenin (**1**).

Plant species	Family	Parts used	Yield (%)	Reference
Arctostaphylos uva-ursi	Ericaceae	Leafy shoot	0.0303	[12]
Ardisia colorata	Myrsinaceae	Fruit	0.0043	[13]
Ardisia creanta	Myrsinaceae	Root	2.3250	[14-16]
Ardisia elliptica	Myrsinaceae	Unknown	-	[17]
Ardisia gigantifolia	Myrsinaceae	Rhizome	0.0148	[18]
Ardisia japonica	Myrsinaceae	Aerial	0.0225	[19,20]
Ardisia punctata	Myrsinaceae	Root	-	[21]
Arisaema franchetianum	Araceae	Tuber	0.0001	[22]
Astilbe chinensis	Saxifragaceae	Rhizome	0.0397	[23,10,24]
Astilbe myriantha	Saxifragaceae	Unknown	-	[25]
Astilbe rivularis	Saxifragaceae	Rhizome	0.0002	[26,27]

Astilbe thunbergii	Saxifragaceae	Rhizome	0.4953	[28,29]
Bergenia cordifolia	Saxifragaceae	Leaf	-	[30-32]
Bergenia cordifolia	Saxifragaceae	Rhizome	0.5688	[33]
Bergenia crassifolia	Saxifragaceae	Rhizome	3.3632	[34,3,5]
Bergenia crassifolia	Saxifragaceae	Leaf	-	[35]
Bergenia ligulata (*ciliata*)	Saxifragaceae	Rhizome	0.0760	[36-42]
Bergenia purpurascens	Saxifragaceae	Rhizome	1.5935	[43,44]
Bergenia scopulosa	Saxifragaceae	Rhizome	-	[45,46]
Bergenia stracheyi	Saxifragaceae	Whole plant	-	[47,48]
Bergenia stracheyi	Saxifragaceae	Rhizome	2.0425	[49,50]
Brachystemma calycinum	Caryophyllaceae	Aerial	0.0002	[51]
Caesalpinia decapetala	Fabaceae	Root	0.0001	[52]
Caesalpinia digyna	Fabaceae	Root	0.0650	[53-57]
Caesalpinia mimosoides	Fabaceae	Root	0.0088	[58]
Cenostigma gardnerianum	Leguminosae	Stem bark	0.0747	[59]
Cenostigma macrophyllum	Leguminosae	Stem bark	0.0747	[60]
Cimicifuga foetida	Ranunculaceae	Rhizome	0.0125	[61,62]
Connarus monocarpus	Connaraceae	Root	-	[63]
Corylopsis coreana	Hamamelidaceae	Leaf	0.8611	[64]
Corylopsis spicata	Hamamelidaceae	Bark	-	[3,65]
Corylopsis willmottiae	Hamamelidaceae	Whole plant	0.0040	[66]
Diospyros Sanja-Minika	Ebenaceae	Wood	3.6402	[67]
Dipterocarpus grandiflorus	Dipterocarpaceae	Stem	0.1600	[68]
Dryobalanops aromatica	Dipterocarpaceae	Stem bark	0.0025	[69,70]
Dryobalanops sp.	Dipterocarpaceae	Heartwood	-	[71]
Endopleura uchi	Humiriaceae	Bark	1.1347	[72-74]
Endopleura uchi	Humiriaceae	Fruit	-	[75]
Ficus racemosa	Moraceae	Bark	-	[76-79]
Flueggea microcarpa	Euphorbiaceae	Leaf	-	[80-82]
Fluggea virosa	Euphorbiaceae	Aerial	-	[83-85]
Garcinia malaccensis	Clusiaceae	Stem bark	0.0012	[86]
Gendarussa vulgaris	Acanthaceae	Aerial	0.0003	[87]
Glochidion obliquum	Euphorbiaceae	Leaf	0.0023	[88]
Glochidion obovatum	Euphorbiaceae	Leaf	0.0006	[89]
Hopea sangal	Dipterocarpaceae	Stem bark	0.0017	[90]
Hopea utilis	Dipterocarpaceae	Stem wood	0.1800	[91]
Humiria balsamifera	Humiriaceae	Aerial	-	[9,92]
Macaranga peltata	Euphorbiaceae	Bark	0.4500	[93]
Mallotus anisopodus	Euphorbiaceae	Aerial	0.0002	[94]
Mallotus japonicus	Euphorbiaceae	Bark	0.8796	[95-99]
Mallotus japonicus	Euphorbiaceae	Cortex	1.9500	[100-102]
Mallotus philippinensis	Euphorbiaceae	Leaf	0.0001	[103]
Mallotus philippinensis	Euphorbiaceae	Stem bark	0.6500	[104-107]
Mallotus repandus	Euphorbiaceae	Stem	0.0380	[108,109]
Mallotus roxburghianus	Euphorbiaceae	Leaf	0.0075	[110]
Peltiphyllum peltatum	Saxifragaceae	Rhizome	0.0092	[111]
Peltoboykinia watanabei	Saxifragaceae	Rhizome	-	[112]
Peltophorum africanum	Fabaceae	Stem bark	1.2000	[113-116]
Peltophorum africanum	Fabaceae	Root	2.0000	[116]
Peltophorum ferruginium	Fabaceae	Bark	-	[117]
Peltophorum inerme	Fabaceae	Flower	-	[118]
Peltophorum pterocarpum	Fabaceae	Flower	0.1008	[119,120]

Peltophorum pterocarpum	Fabaceae	Wood	0.0211	[121]
Pentaclethra macrophylla	Mimosaceae	Root	0.0004	[122]
Phyllanthus columnaris	Euphorbiaceae	Root bark	0.0014	[123]
Phyllanthus flexuosus	Euphorbiaceae	Stem bark	-	[124]
Phyllanthus wightianus	Euphorbiaceae	Whole plant	-	[125]
Pulicaria wightiana	Compositae	Aerial	0.0007	[126]
Pulsatilla koreana	Ranunculaceae	Root	0.0001	[127]
Rivea hypocrateriformis	Convolvulaceae	Stem	0.0070	[128]
Rodgersia aesculifolia	Saxifragaceae	Rhizome	-	[129]
Rodgersia pinnata	Saxifragaceae	Unknown	0.0001	[130]
Rodgersia sambucifolia	Saxifragaceae	Root	3.1250	[16]
Sacoglottis gabonensis	Humiriaceae	Bark	0.0500	[131-135]
Sacoglottis uchi	Humireaceae	Bark	0.1000	[136]
Saxifraga melanocentra	Saxifragaceae	Aerial	-	[137]
Saxifraga stolonifera	Saxifragaceae	Aerial	-	[138-141]
Securinega melanthesoides	Euphorbiaceae	Leaf	-	[142]
Securinega virosa	Euphorbiaceae	Leaf	0.0122	[143]
Shorea leprosula	Dipterocarpaceae	Heartwood	-	[144]
Shorea robusta	Dipterocarpaceae	Leaf	0.0750	[145]
Shorea robusta	Dipterocarpaceae	Root	-	[146]
Streptocaulon griffithii	Asclepiadaceae	Root	0.0022	[147]
Teramnus labialis	Fabaceae	Aerial	-	[148]
Tridax procumbens	Heliantheae	Aerial	0.0017	[149]
Tripterospermum chinense	Gentianaceae	Aerial	-	[150]
Vateria indica	Dipterocarpaceae	Leaf	0.2600	[151,152]
Vateria indica	Dipterocarpaceae	Seed	-	[153]
Vateria indica	Dipterocarpaceae	Stem bark	1.7647	[154]
Vatica albiramis	Dipterocarpaceae	Stem	0.0833	[155]
Vatica bantamensis	Dipterocarpaceae	Leaf	0.1100	[156]
Vatica diospyroides	Dipterocarpaceae	Stem	0.0640	[157]
Vatica mangachpoi	Dipterocarpaceae	Leaf	-	[158,159]
Vatica pauciflora	Dipterocarpaceae	Stem bark	0.0840	[160]
Viburnum nervosum	Cappriifoliaceae	Root	-	[161,162]
Woodfordia fruticosa	Lythraceae	Stem	-	[163]

Yield percentage is calculated in dried plant material weight basis and the highest isolated yield is recorded from the available data.

As can be seen from Table 1, rhizomes of *Ardisia creanata*, *Bergenia crassifolia*, *Bergenia purpurascens*, *Bergenia stracheyi*, *Peltophorum africanum* and *Rodgersia sambucifolia* are the major sources of bergenin (**1**). Barks of *Diospyros Sanja-Minika*, *Endopleura uchi*, *Mallotus japonicus*, *Peltophorum africanum* and *Vatica indica* also contain a high amount of the compound. Leaf of *Corylopsis coreana* is another important source of bergenin. When deposition of bergenin is high in the plant material, simple extraction with acetone, methanol or water followed by concentration and crystallization could be efficient for its isolation [5,97,124,154]. Otherwise, Soxhlet extraction followed by silica gel column chromatography is often employed for the isolation of bergenin. However, the conventional method alone is not efficient to isolate bergenin since repeated silica gel column chromatography, the use of expensive reversed phase adsorbents, preparative high performance liquid chromatography (HPLC) and/or recrystalizations are often essential [19,43,49,64,101,128]. A rapid extraction and purification of bergenin by microwave-assisted extraction coupled with high-speed counter-current chromatography (HSCCC) was reported by Deng et al., in which sample was extracted with 60% aqueous methanol with solvent/sample ratio of 10/1

(mL/g) at 60 ˚C for 15 min followed by direct HSCCC purification [16]. This method was found efficient but limited to small scale. Recently, we have reported an efficient, simple methodology for purification of bergenin (**1**) from *Bergenia purpurascens* rhizome extract through column chromatography using alumina as an adsorbent [44]. Utilizing this protocol, bergenin can be isolated exclusively. MAE/HSCCC

3. Ethnomedicinal values of bergenin

Bergenin (and its congeners) occur in a large number of plants and is considered as an active ingredient in the plant extracts. Bergenin containing herbs have been used as a folk medicine in Asia (India, China including Nepal) since at least the 7th century [164-168]. It is one of the active pharmaceutical ingredients of Ayurvedic herbal drugs and formulations [169]. In Ayurvedic formulations, bergenin containing plant materials such as *Bergenia ligulata* is used in lithiasis, dysuria and polyuria; *Caesalpinia digyna* is used as astringent and antipyretic; *Peltophorum pterocarpum* is used for dysentery and muscular pains; *Vateria indica* is considered to be effective against bronchitis, gonorrhea and syphilis; *Woodfordia fruticosa* is used as tonic and sedative; etc. Reviews on the ethnomedicinal values of bergenin containing plant materials have highlighted the importance of bergenin [2,164,170-179].

4. Pharmacology on bergenin

4.1. Evaluation in infectious diseases

Antibacterial activity

Bergenin (**1**) was found ineffective against *Escherichia coli*, *Salmonella enteritidis*, *Shigella sonnei*, *Pseudomonas aeruginosa*, *Serratia marcenses*, *Klebsiella pneumoniae*, *Salmonella paratyphi*, *Salmonella typhi*, *Salmonella typhimurium*, *Shiegella flexneri*, *Proteus vulgaris*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Bacillus subtilis* and *Erwinia* sp. [44,50,72,120]. Inhibitory effect of bergenin on *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Beta streptococcus* and *Aeruginosus bacillus* was reported [180]. Antitussive effect of bergenin has been reported elsewhere [181,182].

Antiviral activity

Piacente et al. reported a weak anti-HIV-1 activity of bergenin (**1**) in C8166 cells infected with HIV-1_{MN} (X4 virus) with an effective concentration (EC_{50}) value of 40 μg/mL. And, bergenin inhibited the binding of GP120 to sCD4 in a dose-dependent manner [19]. On NS3 serine protease activity assay, bergenin has displayed a weak activity against Hepatitis C virus (IC_{50} = 1.71 mM) [137]. Antiviral activity of bergenin against herpes simplex virus type-1 showed an IC_{50} value of <6.25 μg/mL [27]. Bergenin had no inhibitory property against HIV-1 reverse transcriptase and integrase [114].

Antifungal activity

Bergenin (**1**) displayed antifungal activity against *Candida albicans*, *Candida tropicalis* and *Candida guilliermondii* with MIC values of 14.9, 14.9 and 29.8 μM, respectively, while a lower activity was observed against filamentous fungi *Aspergillus flavus*, *Aspergillus nidulans* and *Aspergillus niger* [72]. Antifungal activity of bergenin against *Trichophyton mentagrophytes* (MIC 250 μg/mL), *Epidermophyton floccosum* (MIC 500 μg/mL), *Trichophyton rubrum* (MIC 500 μg/mL), *Aspergillus niger* (MIC 500 μg/mL) and *Botrytis cinerea* (MIC 250 μg/mL) was reported by Raj et al. [120]. The monosodium salt of bergenin, obtained by treating bergenin with one molar equivalent of NaOH in water, was found effective against *Alternaria alternate*, *Alternaria brassicae*, *Alternaria carthami*, *Fusarium udum*, *Fusarium oxyporum* f. sp. *ciceri*, *Curvularia lunata* and *Erysiphe pisi* [183].

Wound healing effect

Effective dose (ED_{50}) of bergenin (**1**) for burn wound healing was found to be 190 μg/wound in mice [29]. Wound healing effect of bergenin was also reported by Mukherjee et al. [145].

4.2. Evaluation as antiparasitics and insecticides

Antiplasmodial activity

Bergenin (**1**) displayed a good activity with IC_{50} value of 2.4 μg/mL against chloroquine sensitive strain of *Plasmodium falciparum* (D10) indicating it is a new potential antimalarial agent [42].

Antifeedent activity

Bergenin (**1**) exhibited significant antifeedant activity against lepidopterous insects [26].

Trypanocidal activity

Bergenin (**1**) showed an inhibitory effect on the growth of *Trypanosoma brucei* with an IC_{50} value of 1 mM [84].

4.3. Evaluation in immunological and inflammatory diseases

Antiinflammatory activity

Swarnalakshmi et al. have reported that bergenin (**1**) produces a dose dependent inhibition of carrageenin induced rat paw oedema [119]. Nazir et al. have reported antiarthritic activity of bergenin in adjuvant-induced arthritic balb/c mice [49]. A flow cytometric study revealed that bergenin inhibits the production of proinflammatory Th1 cytokinases (IL-2, IFN-γ and TNF-α) and promotes the production of Th2 cytokines (IL-4 and IL-5). De Oliveira et al. have reported antinociceptive and antiinflammatory properties of bergenin owing to the inhibition of IL-1β and TNF-α release [59]. Nunomura et al. reported antiinflammatory effect of bergenin against cyclooxygenase 1 (Inhibition concentration (IC_{50}) = 107.2 μM), cyclooxygenase 2 (IC_{50} = 1.2 μM) and phospholipase A_2 (IC_{50} = 156.6 μM) [73]. Jachak et al. have reported that bergenin was an inhibitory principle in the ethyl acetate extract of *Tridax procumbens* for antiinflammatory effect [149]. Antiinflammatory activity of bergenin against 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation in mice was evaluated by Zhang et al. [121]. Bergnein displayed a low percent inhibitory ratio (34 ± 4.7% at 0.5 mg/ear) compared to indomethacin (96 ± 4.7% at 1.0 mg/ear).

Antihepatotoxic activity

The hepatoprotective effect of bergenin (**1**) utilizing CCl_4-induced rat hepatocytes was initially reported by Hikino et al. [184]. Kim et al. reported bergenin reduces the levels of glutamic pyruvic transaminase (GPT) and sorbitol dehydrogenase (SDH) in the culture medium released from the CCl_4-intoxicated rat hepatocytes [101]. The release of GPT and SDH was blocked 62.1% and 49.9% respectively at 100 μM concentration of bergenin. The antihepatotoxicity of bergenin was also evidenced by recovering of glutathione content (up to 25.3%), and elevating the activities of glutathione S-tranferase (up to 51.5%) and glutathione reductase (up to 29.1%) at 300 μM concentration. The release of GPT and SDH was blocked by bergenin on D-galactosamine-intoxicated rat hepatocytes. At the same time, DNA synthesis was increased indicating liver protection activity of bergenin [185,186,99]. It was found that enzymatic activities of alanine/aspartate aminotransferase, sorbitol dehydrogenase, γ-glutamyltransferase, glutathione S-transferase and glutathione reductase were restored towards normalization in the experimental models after oral administration of bergenin.

Rats pretreated with bergenin significantly reduced 2,4-dinitrophenyl hydrazine-induced lipid peroxidation in the liver, brain and red blood cell [134,135].

4.4. Evaluation in blood and cardiovascular diseases

Platelet aggregation inhibition

Bergenin (**1**) inhibited platelet aggregation in human blood [86]. It showed marked inhibitory effect caused by the three inducers arachidonic acid (IC_{50} = 240.6 μM), adenosine diphosphate (IC_{50} = 120.3 μM) and collagen (IC_{50} = 60.9 μM).

Antiarrhythmic activity

Bergenin (**1**) has shown efficacy in restoring sinus rhythm in $BaCl_2$-induced arrhythmic rats, and it has shortened the duration of ventricular premature beat, tachycardia and fibrillation after ligation and reperfusion [83]. Bergenin could increase the atria fibrillation threshold in urethane induced anesthetized rabbits indicating its potentiality to treat cardiac arrhythmias.

4.5. Evaluation in oncological diseases

Anticancer activity

Bergenin (**1**) showed a weak activity (IC_{50} = 44 μM) against the Murine Breast Cancer Cell Line, FM3A [13]. Growth inhibition of HepG2 cells was achieved [187]. Anti-proliferative effects of bergenin on human prostrate cancer cell lines LNCaP and DU145 were studied [64]. The cytotoxic activity of bergenin against several cell lines was also studied by Wibowo et al. [69] and Xue et al. [24]. Bergenin has exhibited inhibitory effects against *Epstein-Barr* virus early antigen (EBV-EA) activation induced with TPA in *Raji cells* and against skin tumor promotion in mouse skin carcinogenesis [121]. It exhibited melanogenesis inhibitory activity in α-melanocyte-stimulating hormone (α-MSH)-stimulated B 16 melanoma cells therefore may be valuable as the potential skin whitening agents. Bergenin exhibited protection effect in γ-radiation induced DNA (pBR322) damage [55]. No antitumor activity of bergenin on human gastric carcinoma cell line MGC-803 was reported [52].

Antioxidant activity

Reactions of pulse radiolytically generated hydroxyl (•OH) radicals with bergenin have been studied, which showed that bergenin radical products are formed by •OH radical addition to the phenyl ring and H-atom abstraction from the C ring in bergenin [188]. In most of the cases, •OH radical reacts with natural polyphenols to produce phenoxyl radicals, in contrast, in the case of bergenin, reducing radical adducts are the major transients formed, which may react with oxygen forming peroxyl type radicals. Therefore, bergenin may not act as a potent antioxidant in preventing free radical induced oxidative damage; however, may act as a pro-oxidant and exhibit antitumor activity. Theoretical calculations on the formation of the radical derivatives of bergenin using •H, •OH, $•CH_3$ and $•CCl_3$ revealed that the methoxy group at 6-position is the most favourable site for a radical attack [136]. To confirm antioxidant activity of bergenin, β-carotene, DPPH and a heterogeneous Fenton assays were carried out.

Bergenin (**1**) itself is a good scavenger of hydroxyl radicals but not so effective in scavenging other free radicals like superoxide radical and DPPH [33,35,41,42,50,52,55,64,110,111,148,188,189]. Significant antioxidant activity of bergenin in hydrogen peroxide, ABTS, DPPH and inhibition of lipid peroxidation assays with IC_{50} values 32.54, 75.06, 165.35 and 365.12 μg/mL, respectively was reported by Srinivasan et al. [54]. Bergenin has displayed low antioxidant activity in nitric oxide

method (IC_{50} = 785.63 μg/mL) and deoxy ribose method (IC_{50} = 815.63 μg/mL), and was found to be inactive in scavenging hydroxyl radical by DNA method and superoxide radical by alkaline dimethyl sulfoxide method. DPPH radical scavenging activity of bergenin was also reported by Sumino et al. [13] and Zamarrud et al. [128].

4.6. Evaluation in alimentary tract and metabolic diseases

Gastroprotective activity

Bergenin (**1**) showed a dose dependent antisecretory effect on gastric secretion in pylorus ligated rats and antiulcerogenic activity in stressed rat ulcers [190]. The effectiveness may be due to inhibition of acetylcholine release [191]. Bergenin showed gastroprotective effect by increasing prostaglandin production [192]. It inhibited the bovine adrenal tyrosine hydroxylase activity by 29% at 20 μg/mL concentration [102].

Antidiabetic activity

Bergenin (**1**) at 10 mg/kg oral dose to streptozotocin-nicotinamide induced diabetic rats was found to reduce blood glucose level significantly in oral glucose tolerance test [56]. It reversed plasma lipid profile (total cholesterol, triglycerides and lipoproteins) to normal values, decreased lipid peroxides, and increased superoxide dismultase and catalase in liver illustrating its antidiabetic, hypolipidemic and antioxidant activities in Type 2 diabetic rats. Histopathological studies demonstrated a considerable regenerative effect on the β cells of pancrease attributing a positive effect of bergenin on the endocrine cells to produce insulin. Potentially antidiabetic activity of bergenin was reported by Li et al. since it inhibited human protein tyrosine phosphatase 1B (hPTP1B) activity with IC_{50} value of 157 μM [20].

Urease inhibitor

Bergenin (**1**) was found to inhibit the *Bacillus pasteurii* urease [105]. Urease produced by bacteria such as *Helicobacter pylori* in gastrointestinal tract catalyzes the hydrolysis of urea to produce ammonia and carbon dioxide, and permits bacteria to grow and colonize at the low pH leading gastric and peptic ulceration and associated cancer. Molecular docking study showed that bergenin penetrates into the active site of urease preventing the access to urea, thereby involving in antiulcer activity.

Lipolysis effect (antiobesity activity)

Bergenin (**1**) has enhanced norepinephrine-induced lipolysis in endogeneous lipid droplets, slightly stimulated adrenocorticotrophic hormone-induced lipolysis and inhibited insulin-induced lipogenesis from glucose in fat cells obtained from rat epididymal adipose tissues [28]. Therefore, bergenin may be effective in formulations for the treatment of obesity.

Hypolipidemic activity

Oral administration of bergenin (**1**) to hyperlipidemic rats significantly decreased serum total lipid but not much change in serum cholesterol and triglycerides for 14 days [82]. However after 21 days of feeding, serum cholesterol, triglycerides, low-density lipoprotein-cholesterol levels were significantly reduced, while the serum high-density-cholesterol level was elevated.

4.7. Evaluation in renal diseases

Effect of bergenin (**1**) on urolithiasis induced by 3% glycolic acid in albino rats was evaluated; however, it exhibited less significant antiurolithiatic activity [193].

5. Analysis and estimation of bergenin

Thin layer chromatography (TLC), HPLC and Liquid chromatography-tandem mass spectrometry (LC-MS/MS) techniques have been employed for the estimation of bergenin (**1**) in the plant materials. TLC method was used for the quantification of bergenin in different parts of different *Bergenia* species [194-197,35] and *Mallotus phillippensis* [198]. Several researchers have used HPLC method to determine bergenin in genus *Bergenia* [39,197,199-202], *Endopleura uchi* [73], *Peltophorum pterocarpum* [203], *Ardisia japonica* [204] and *Ficus racemosa* [205,206]. About 3.2% of bergenin was found to be deposited in the rhizomes of *Bergenia ligulata*, *Bergenia ciliata* and *Bergenia stracheyi* [39,199]. Up to 9.77% of bergenin was found to be deposited in the rhizome of *Bergenia purpurascens* distributed in Yulong reservoir of Lijiang County, China [200]. Bark of *Endopleura uchi* contained 3.19% of bergenin [73]. Flower of *Peltophorum pterocarpum* contains 0.40% of bergenin [203]. The amount of bergenin in stem bark of *Ficus racemosa* was estimated by Veerapur et al. and Ahmed and Urooj separately and found to be 0.15% and 0.89%, respectively [205,206].

Pharmacokinetic characterization of the substance is essential during drug development process. Drug absorption, distribution, metabolism and excretion are the key factors for development of effective drug. HPLC method has been employed for the determination of bergenin (**1**) in rat plasma [207,208]. After intravenous administration of bergenin in Wistar rats at the dose of 11.25 mg/kg, blood samples were collected at different intervals [207]. The study of plasma concentration-time curve of bergenin indicated that bergenin distributed widely and eliminated with moderate velocity in rat. On the other hand, when bergenin was given to rats by oral route at a single dose of 22.5 mg/kg, no satisfied plasma concentration data were obtained perhaps indicating that bergenin is easily degraded in the digestive system, including quick metabolism or a poor absorption in gastrointestinal tract. Upon intravenous administration of bergenin to the rats, bergenin was rapidly distributed in blood plasma and eliminated with the half-lives of 3 and 33 min respectively and were not related to the administration doses [208]. Shi et al. reported determination of bergenin in rat urine, feces and tissues after intravenous administration of formulated bergenin at a single dose of 22.5 mg/kg body weight of Wistar rats [209]. The study demonstrated that 35.36% and <10% of bergenin was recovered from urine and feces, respectively. Comparision to the tissues (liver, kidney, lung, heart, spleen and brain) examined, kidney accumulated the highest bergenin concentration and the longest drug resident time, while it was less significantly distributed into the brain owing to its hydrophilic property.

Yu et al. reported quantitation of bergenin and pharmacokinetic study in human plasma by LC-MS/MS [210]. The blood samples from healthy voluenteers were collected at different intervals after oral administration of 250 mg of bergenin. The maximum concentration of 66.6 ng/mL occurred at 2.0 ± 0.9 h and the elimination half-time was 3.7 ± 2.4 h. HPLC-MS/MS method was used by Wang et al. to determine bergenin in human plasma [211]. This method was found to be suitable for the determination of low bergenin concentration (lowest limit of quantification = 0.25 ng/mL) in human plasma after oral administration of bergenin tablet (250 mg) and pharmacokinetic parameters (absorption half life = 0.852 h, time to peak concentration = 2.125 h, maximum plasma concentration = 15.915 ng/mL, elimination half life = 4.198 h etc.) were given. Bergenin content in *Caesalpinia digyna* roots was estimated by LC-MS and found to be contained nearly 30% in the plant extracts [55].

The interatction between bergenin and human serum albumin (HAS) in membrane mimetic environment was studied by Zhang [212]. This study indicated that bergenin bound to HAS mainly by a hydrophobic interaction.

Qin et al. reported that oral bioavailability of the drug can be increased utilizing bergenin-phospholipid complex, which was prepared by refluxing bergenin (**1**) with phospholipid (bergenin to phospholipid ratio = 0.9 w/w) in anhydrous ethanol at 60 ˚C for 2 h. This complex was orally

administered to rats and blood plasma was analyzed by HPLC. The study showed that the relative bioavaolability was signigicantly increased to 439% of bergenin [213].

Voltammetric determination of bergenin was demonstrated by Chen et al. [214]. A 4-(2-pyridylazo)-resorcinaol polymer film modified glassy carbon electrode was used to accumulate bergenin leading enhancement of the oxidation peak current depending on the concentration. This method was used to determine bergenin in tablets and urine samples. The electrocatalytic oxidation of bergenin was also investigated on the surface of a multi-wall carbon nanotubes modified carbon paste electrode to determine the amounts of bergenin in tablets [215].

6. Naturally occurred bergenin derivatives

A list of bergenin derivatives isolated from the plant materials is depicted in Table 2 and the structures of the compounds are shown in Fig. 2.

Table 2
Bergenin derivatives (**2**-**35**) isolated form plants.

Compound isolated	Plant species	Part used	Yield (%)	References
Norbergenin (**2**)	*Ardisia colorata*	Fruit	0.0170	[13]
	Ardisia japonica	Leaf	0.0129	[19]
	Bergenia crassifolia	Root	-	[36,38]
	Caesalpinia digyna	Root	-	[53]
	Corylopsis coreana	Leaf	0.0049	[64]
	Corylopsis spicata	Bark	-	[3]
	Mallotus japonicus	Bark	0.0028	[98]
	Peltophorum africanum	Bark	-	[113]
	Saxifraga stolonifera	Whole plant	-	[139]
	Shorea leprosula	Heartwood	-	[144]
	Woodfordia fruticosa	Stem	-	[163]
8-O-Methylnorbergenin (**3**)	*Saxifraga stolonifera*	Whole plant	0.0004	[216]
4-O-Galloylnorbergenin (**4**)	*Mallotus japonicus*	Bark	0.0005	[98]
11-O-Galloylnorbergenin (**5**)	*Mallotus japonicus*	Bark	0.0147	[97]
	Mallotus japonicus	Bark	0.0004	[98]
Demethoxybergenin (**6**)	*Ardisia colorata*	Fruit	0.0036	[13]
8,10-Di-O-methylbergenin (**7**)	*Ardisia japonica*	Leaf	0.0090	[19]
	Macaranga peltata	Heartwood	0.0133	[93]
3,8,10-Tri-O-methylbergenin (**8**)	*Macaranga peltata*	Heartwood	0.0033	[93]
8,10,11-Tri-O-methylbergenin (**9**)	*Macaranga peltata*	Heartwood	0.0008	[93]
Rivebergenin A (**10**)	*Rivea hypocrateriformis*	Stem	0.0035	[128]
11-O-Acetylbergenin (**11**)	*Flueggea virosa*	Aerial	-	[85]
	Vitis repens	Unknown	-	[217]
4-O-Galloylbergenin (**12**)	*Ardisia gigantifolia*	Rhizome	0.0001	[18]
	Bergenia purpurascens	Root	0.0169	[43]
	Bergenia scopulosa	Rhizome	-	[46]
	Corylopsis willmottiae	Whole plant	0.0031	[66]
	Mallotus japonicus	Bark	0.1730	[97]
	Mallotus japonicus	Bark	0.0173	[98]
	Mallotus philippinensis	Leaf	0.0004	[103]
11-O-Galloylbergenin (**13**)	*Ardisia gigantifolia*	Rhizome	0.0002	[18]
	Astilbe chinensis	Rhizome	0.0006	[24]
	Bergenia ciliata	Root	-	[218]
	Bergenia ligulata	Rhizome	0.0043	[42,219]
	Bergenia purpurascens	Root	0.1084	[43]

	Caesalpinia digyna	Root	0.0032	[57]
	Corylopsis coreana	Leaf	0.0450	[64]
	Corylopsis willmottiae	Whole plant	0.3188	[66]
	Mallotus japonicus	Bark	0.1914	[97]
	Mallotus japonicus	Bark	0.0070	[98]
	Mallotus philippinensis	Stem bark	0.0165	[220]
	Peltiphyllum peltatum	Rhizome	0.0007	[111]
3,4-Di-O-galloylbergenin (**14**)	*Mallotus japonicus*	Bark	0.0008	[98]
3,11-Di-O-galloylbergenin (**15**)	*Bergenia crassifolia*	Root	-	[221]
4,11-Di-O-galloylbergenin (**16**)	*Corylopsis willmottiae*	Whole plant	0.0004	[66]
	Mallotus japonicus	Bark	0.0006	[98]
3,4,11-Tri-O-galloylbergenin (**17**)	*Mallotus japonicus*	Bark	0.0004	[98]
Bergecin A (**18**)	*Bergenia stracheyi*	Whole plant	0.0001	[48]
Bergecin B (**19**)	*Bergenia stracheyi*	Whole plant	0.0001	[48]
10-O-(p-Hydroxybenzoyl)bergenin (**20**)	*Saxifraga melanocentra*	Aerial	-	[137]
11-O-(p-Hydroxybenzoyl)bergenin (**21**)	*Astilbe chinensis*	Rhizome	0.0002	[24]
	Vatica bantamensis	Leaf	0.0005	[156]
11-O-Vanilloylbergenin (**22**)	*Ardisia crenata*	Root	-	[15]
	Vatica bantamensis	Leaf	0.0007	[156]
11-O-(3'-O-methylgalloyl)bergenin (**23**)	*Ardisia gigantifolia*	Rhizome	0.0002	[18]
	Astilbe chinensis	Rhizome	0.0013	[24]
	Corylopsis willmottiae	Whole plant	0.0001	[66]
11-O-(4'-O-Methylgalloyl)bergenin (**24**)	*Crassula* cv. 'Himaturi'	Whole plant	0.0735	[222]
	Saxifraga melanocentra	Aerial	-	[223]
11-O-(3',4'-Di-O-methylgalloyl)bergenin (**25**)	*Ardisia crenata*	Root	-	[15]
11-O-Veratroylbergenin (**26**)	*Ardisia gigantifolia*	Rhizome	0.00015	[18]
11-O-Syringylbergenin (**27**)	*Ardisia crenata*	Root	-	[15]
	Ardisia gigantifolia	Rhizome	0.0002	[18]
	Corylopsis willmottiae	Whole plant	0.0005	[66]
	Vatica bantamensis	Leaf	0.0002	[156]
11-O-(E)-p-Coumaroylbergenin (**28**)	*Peltophorum africanum*	Bark	-	[113]
	Vatica bantamensis	Leaf	0.0002	[156]
11-O-(Z)-p-Coumaroylbergenin (**29**)	*Vatica bantamensis*	Leaf	0.0005	[156]
11-O-(E)-Caffeoylbergenin (**30**)	*Securinega virosa*	Leaf	0.0039	[143]
11-O-(E)-Ferulaylbergenin (**31**)	*Vatica bantamensis*	Leaf	0.0002	[156]
11-O-(Z)-Ferulaylbergenin (**32**)	*Vatica bantamensis*	Leaf	0.0001	[156]
11-O-(E)-Sinapoylbergenin (**33**)	*Vatica bantamensis*	Leaf	0.0011	[156]
Rivebergenin B (**34**)	*Rivea hypocrateriformis*	Stem	0.0049	[128]
Dimer of bergenin (**35**)	*Astilbe rivularis*	Rhizome	0.0010	[27]

Percentage of isolated yield is recorded in dried plant material weight basis from the available data.

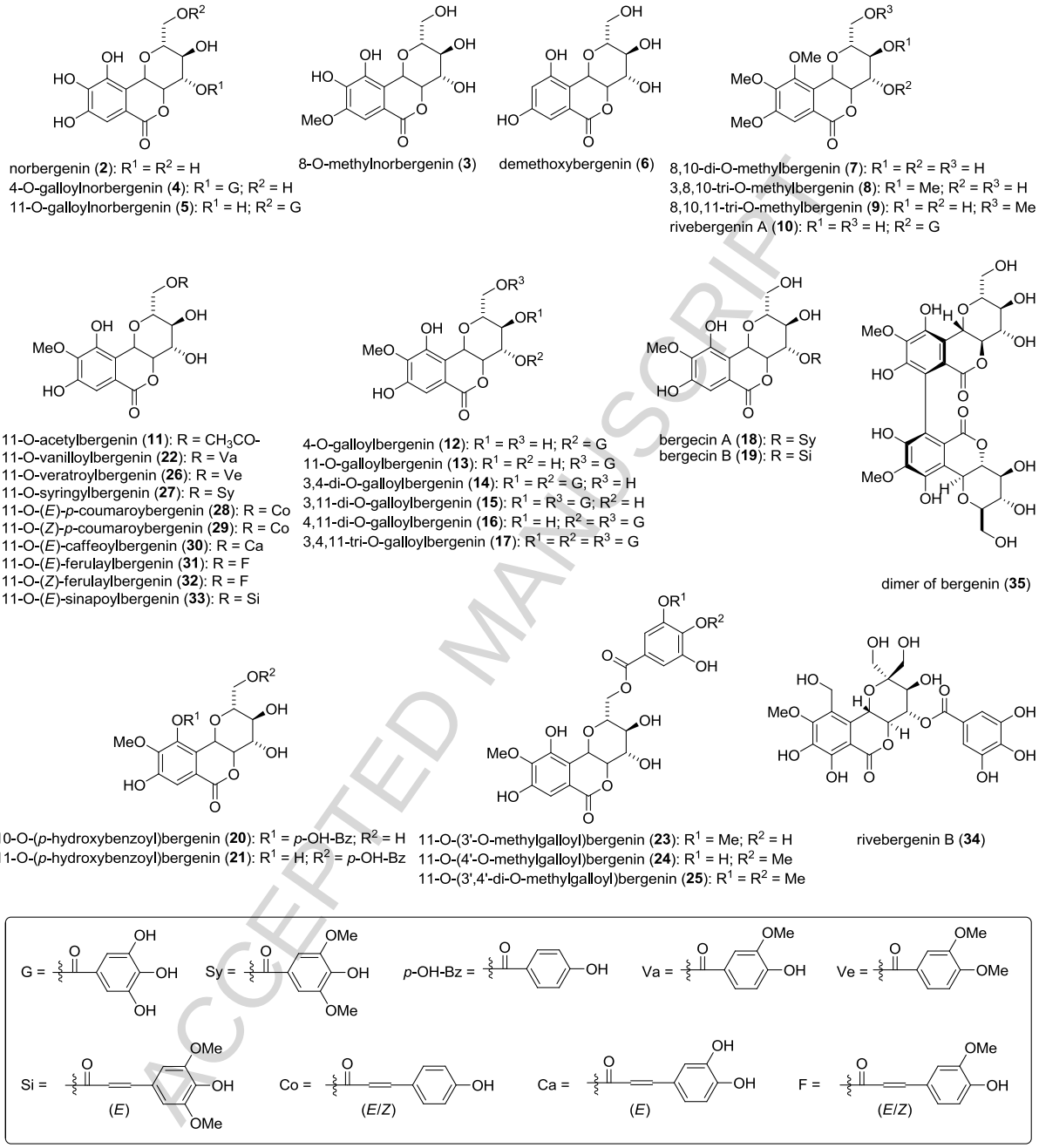


Fig. 2. Bergenin derivatives (**2**-**35**) isolated from the plant materials.

Norbergenin (**2**) has shown to have antioxidant [224,13], gastroprotective [192,102], anti-HIV [19], and antiarthritic [49] activities. 11-O-Acetyl bergenin (**11**) showed antitrypanosomal activity with IC_{50} value of 0.17 mM against trypomastigotes of *Trypanosoma evansi* [217]. DPPH free-radical scavenging activity of 11-O-galloylbergenin (**13**) [111,42,18]; 4-O-galloylbergenin (**12**), 11-O-(3'-O-methylgalloyl)bergenin (**23**), 11-O-veratroylbergenin (**26**) and 11-O-syringylbergenin (**27**) [18]; rivebergenin A (**10**) and rivebergenin B (**34**) [128]; bergecin A (**18**) and bergecin B (**19**) [48]; 11-O-(4'-O-methylgalloyl)bergenin (**24**) [222]; and 11-O-(*E*)-caffeoylbergenin (**30**) [143] were reported. Arfan et al. have reported 11-O-galloylbergenin (**13**) possesses analgesic and antiinflammatory activities against formalin-induced noxious pains and carrageenan-induced paw oedema in rats, respectively [220]. It was also found more potent in the total antioxidant phosphomolybdate assay, reducing power assay and antiplasmodial assay [42]. Selective α-glucosidase inhibitory activity of compound **13** was reported [111]. 3,11-Di-O-galloylbergenin (**15**) has displayed a moderate antilipid

droplet accumulation activity [221]; 11-O-(4'-O-methylgalloyl)bergenin (**24**) inhibited arachidonic acid-induced platelet aggregation more efficiently than acetylsalicylic acid [222]; and bergecin B (**19**) showed potent inhibitory potential against the enzyme lipoxygenase (IC_{50} = 24.3 μM) [48]. Antiviral efficacy (IC_{50} = 25 μg/mL) of the dimer compound **35** was reported [27].

7. Derivatization of bergenin

7.1. Alkylation

Starting from bergenin (**1**), bergenin pentamethyl ether (**36**) was prepared using methyl iodide and freshly prepared Ag_2O in DMF [93]. 8,10-Di-O-methylbergenin (**7**) was synthesized by methylation of bergenin (**1**) and norbergenin (**2**) with diazomethane [97,139]. Shah et al. have prepared the alkyl derivatives of bergenin (**7**, **37**-**50**) by treating alkyl halides with bergenin (**1**) under mild basic conditions [107] (Fig. 3). The alkyl derivatives **7**, **40** and **50** showed nitric oxide inhibitory activity; **40** and **50** were TNF-α inhibitors; and **43**, **48** and **50** exhibited moderate antiinflammatory activity.

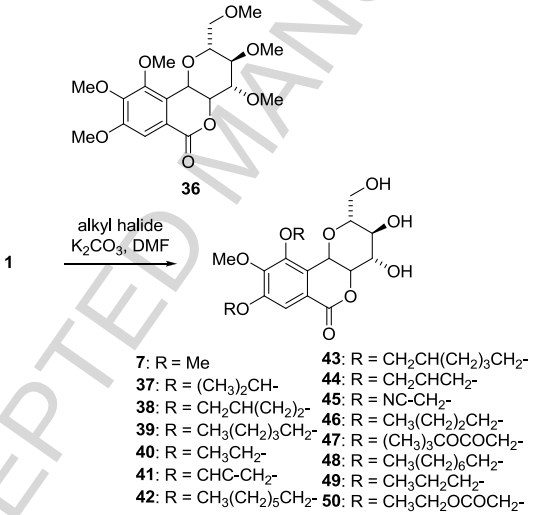


Fig. 3. Alkyl derivatives of bergenin.

7.2. Acylation

Several researchers have synthesized pentaacetylbergenin (**51**) by treating bergenin (**1**) with acetic anhydride or acetyl chloride in the presence of a base (such as pyridine, triethyl amine, DMAP, etc.) [5,49,50,74,93,99,124,162,225]. The acetylbergenin (**51**) has exerted hepatoprotective activity against D-galactosamine-induced cytotoxicity in cultured rat hepatocytes, and restored glutathione levels and decreased activities of glutathione S-transferase and glutathione reductase [226,99]. Antinociceptive activity of the acetylbergenin in mice was also reported [74]. Using different acid chlorides, bergenin acylates (**51**-**54**) were synthesized by Jung et al. [225] (Fig. 4). Comparing to the parent bergenin (**1**), these derivatives (**51**-**54**) possessed enhanced antiinflammatory activity (suppression of lipopolysaccharide (LPS)-induced nitric oxide generation) and antinarcotic effects on morphine dependence in mice.

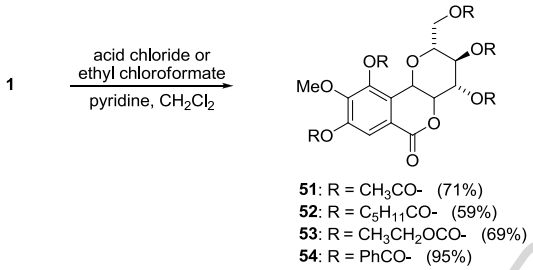


Fig. 4. Preparation of bergenin pentaacylates [225].

Tiwari and Khosa have prepared bergenin diethyl ether triacetate (**55**) in two steps: ethylation of phenolic groups of bergenin followed by acetylation of alcoholic groups (Fig. 5) [162].

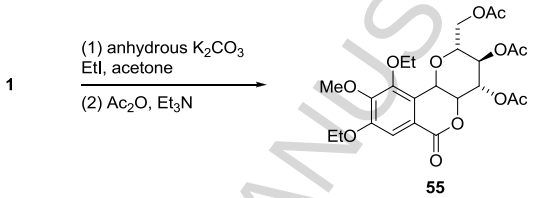


Fig. 5. Preparation of bergenin diethyl ether triacetate (**55**) [162].

Kumar et al. have synthesized bergenin monoacylates (**13**, **22**, **57**) by coupling of acid chlorides with dibenzyl bergenin (**56**) followed by hydrogenation (Fig. 6) [106]. Compounds **13** and **57** exhibited potent antiglycation activity with the IC_{50} values of 12.28 and 60.75 μM, respectively. According to the authors, formation of fluorescent advanced glycation end products associated with secondary diabetes complications occurs in three stages – formation of Schiff-bases, Amadori rearrangement and decarbonyls formation together with cross linking with proteins. 11-O-Galloylbergenin (**13**) has been displayed potent inhibitory activities at all the three stages.

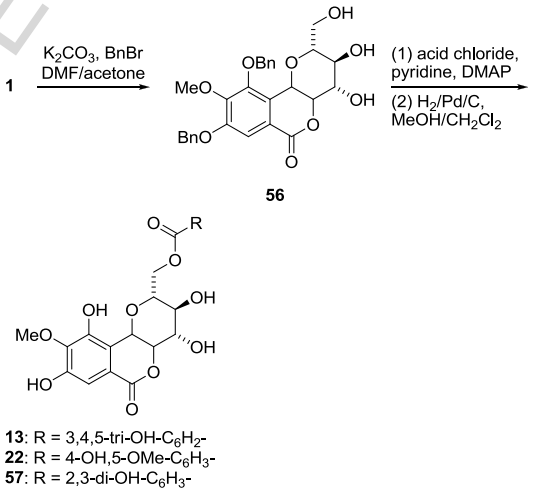


Fig. 6. Preparation of bergenin monoacylates [106].

7.3. Demethylation

Demethylation of bergenin (**1**) using HI yielded norbergenin (**2**) [139]. Norbergenin (**2**) was also synthesized by acetylation of bergenin followed by demethylation with BCl_3 and deprotection of hydroxyls [224,49] (Fig. 8). Pouységu et al. reported chemoselective oxygenative O-demethylation of phenolic methyl aryl ethers of bergenin (**1**) and its monobenzyl derivatives (**58**, **59**) (monobenzylation of the phenolic group of bergenin was achieved by treating with benzyl chloride in the presence of

$NaHCO_3$ and NaI in DMF) using stabilized 2-iodoxybenzoic acid (SIBX) afforded demethylated products norbergenin (**2**) and its monobenzylated catacholic derivatives (**60**, **61**) (Fig. 7) [116].

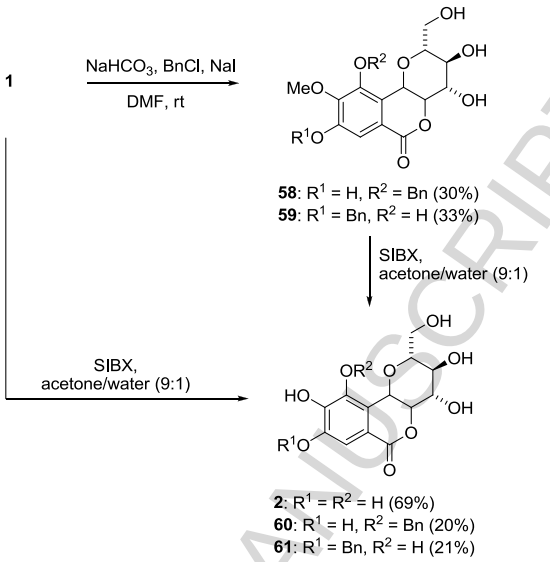


Fig. 7. Monobenzylation of bergenin and demethylation [116].

7.4. Selective monoesterification

Takahashi et al. converted bergenin (**1**) into norbergenin (**2**) and then modified the sugar part by coupling with a variety of fatty acids (Fig. 8) [224]. Selective benzylation of the phenolic hydroxyl groups in norbergenin (**2**) afforded tribenzyl norbergenin (**62**). The hydroxyl groups on the sugar part were then esterified with various chain lengths of fatty acids to give compounds **63**-**68**. Monoesterification of the hydroxyl group at C-11 position was accomplished by coupling **62** with DCC and hexanoic acid followed by hydrogenation to obtain norbergenin 11-caproate (**69**). Norbergenin 4-caproate (**70**) was prepared by protection of hydroxyl groups at C-11 and C-3 as an acetal, esterification at free C-4 followed by hydrogenation. Norbergenin 3-caproate (**71**) was obtained by acid hydrolysis of compound **65**. These derivatives (**63**-**71**) greatly enhanced the free radical scavenging activity and prevented neuronal death of fetal rat cortical neurons, caused by reactive oxygen species, in Dulbeco's modified Eagle's medium (DMEM) supplemented with N2.

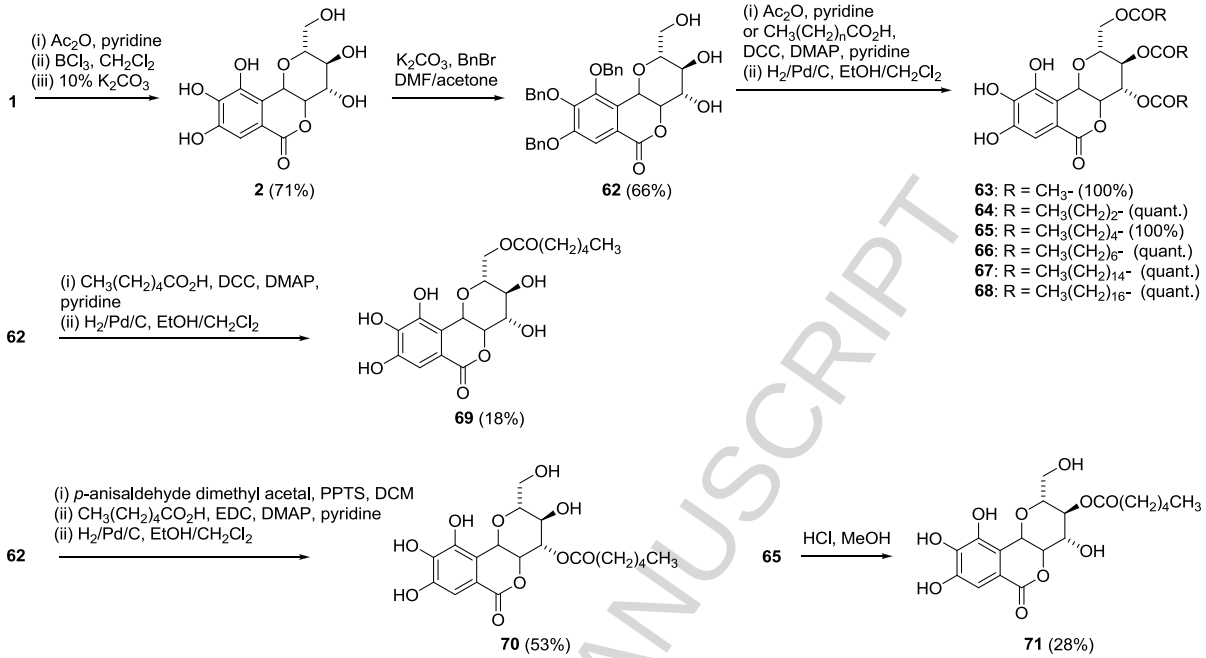


Fig. 8. Selective esterification [224].

Nazir et al. prepared bergenin pentaacetate (**51**) by acetylation of bergenin (**1**) and was subjected to lipase (PSL, lipase from *Pseudomonas cepacia* immobilized on Hyflo Super Gel or MML, lipase from *Mucor miechei* immobilized in Sol-Gel-AK)-catalyzed regioselective alcoholysis in dry n-butanol to obtain 3,4,10,11-tetraacetate of bergenin (**72**) (Fig. 9) [50]. The free-hydroxyl group of compound **72** was acylated with various fatty acids by reacting with DCC in the presence of DMAP to yield acyl derivatives **73-76**. Compounds **51** and **73** showed DPPH radical scavenging activity; compounds **51**, **72** and **73** showed considerable antibacterial activity; and compounds **75** and **76** were found to promote xanthine oxidase catalyzing ability against xanthine to produce uric acid.

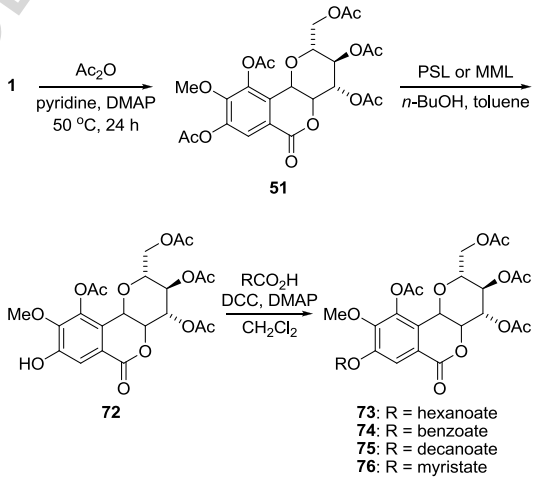


Fig. 9. Acetylation, alcoholysis and esterification of bergenin [50].

Mozhaev et al. [227] demonstrated a combinatorial strategy for the sequential acylations of bergenin (**1**) employing immobilized lipases (Chirazyme L-2, Chirazyme L-9, lipase PS30 and lipase FAP-15) and protease (Subtilisin Carlsberg) at 11 and 4 positions, respectively (Fig. 10). Regioselective deacylation at 11 position was achieved when the diacylated product was hydrolysed with the lipase

in acetonitrile containing 2% water. A set of twelve acyl donors including vinyl and trifluoroethyl esters were used to prepare a library of 24 monoacylated and 144 diacylated derivatives of bergenin.

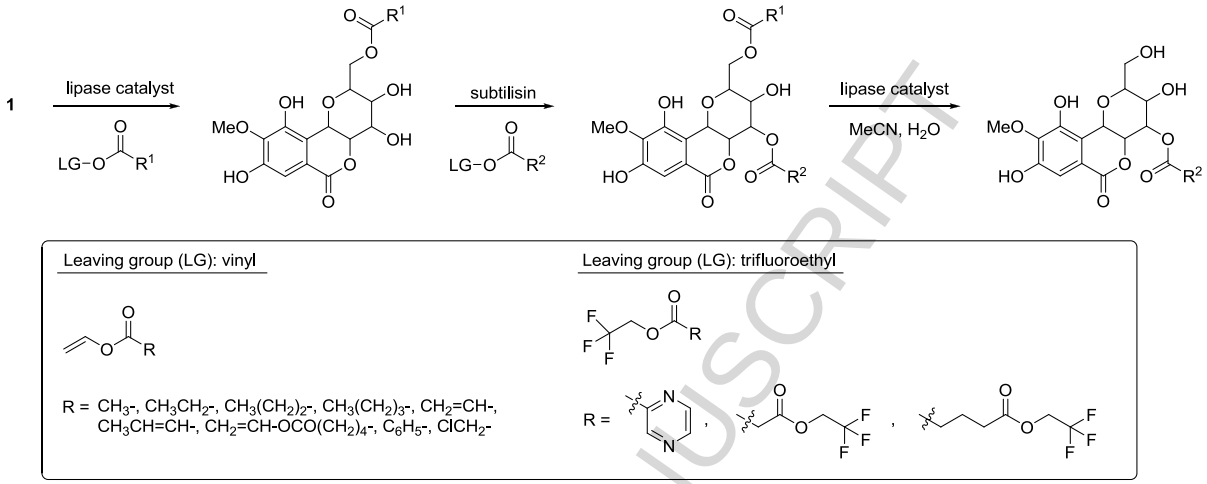


Fig. 10. Sequential enzymatic acylation/hydrolysis for production of acylated bergenin derivatives [227].

7.5. Esterification of the primary hydroxyl under Mitsunobu conditions

Kumar et al. synthesized bergenin esters (**77**-**84**) by coupling of aromatic acids with bergenin (**1**) employing Mitsunobu conditions and their potentiality for free radical $ABTS^{\bullet+}$ scavenging were reported. (Fig. 11) [106].

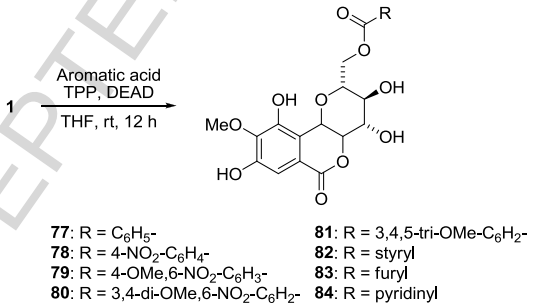
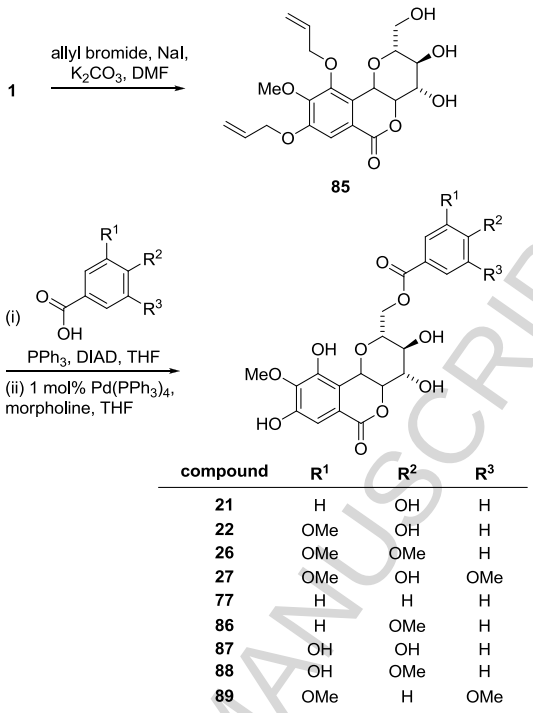


Fig. 11. Synthesis of bergenin esters [106].

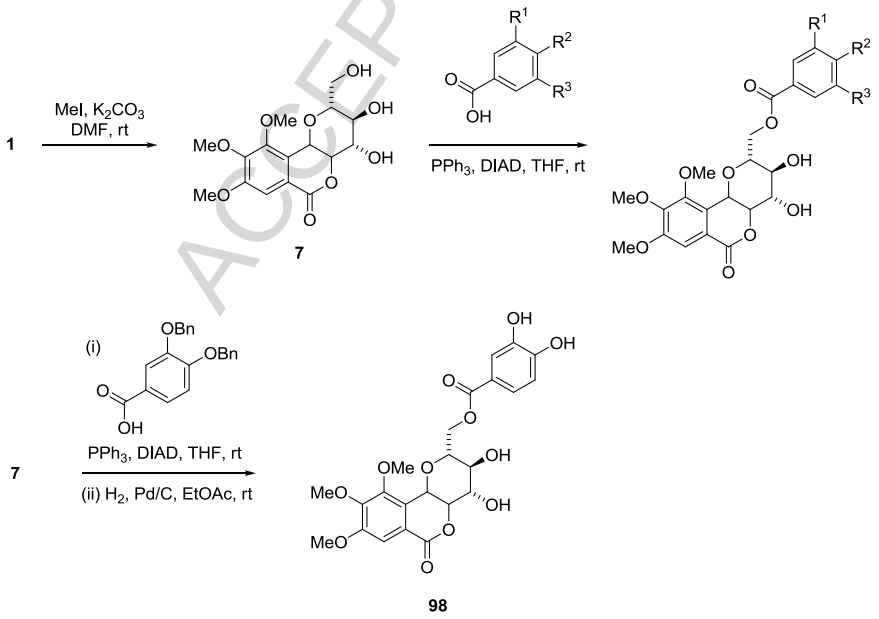
Bergenin esters (**21**,**22**,**26**,**27**,**77**,**86**-**89**) were prepared by Kashima and Miyazawa (Fig. 12), and their mushroom tyrosinase inhibitory and antioxidant activities were reported [40]. Among them compound 11-O-protocatechuoylbergenin (**87**) exhibited potent tyrosinase inhibitory activity (IC_{50} = 17.5 μM). These compounds were also evaluated for β-secretase (BACE1) activity [41]. Among them, compound **87** was the most potent inhibitor with an IC_{50} value of 0.6 μM. Other analogy compounds **22**, **26** and **88** displayed IC_{50} values of <10.0 μM in BACE1 inhibitory activity.



compound	R^1	R^2	R^3
21	H	OH	H
22	OMe	OH	H
26	OMe	OMe	H
27	OMe	OH	OMe
77	H	H	H
86	H	OMe	H
87	OH	OH	H
88	OH	OMe	H
89	OMe	H	OMe

Fig. 12. Synthesis of bergenin esters [40].

In a subsequent paper, Kashima and Miyazawa have prepared di-O-methylbergenin analogues (**90**-**98**) starting from bergenin (**1**) and their antioxidant property and tyrosinase inhibitory activity were studied (Fig. 13) [228]. Among tested analogues, compound **98** exhibited a greater antioxidant activity and tyrosinase inhibitory activity (IC_{50} = 9.1 μM).



compound	R^1	R^2	R^3
90	H	H	H
91	H	OH	H
92	H	OMe	H
93	OMe	OMe	H
94	OMe	OH	H
95	OH	OMe	OMe
96	OMe	H	OMe
97	OMe	OH	OMe

Fig. 13. Synthesis of di-O-methylbergenin esters [228].

7.6. Dimerization

Wang et al. have reported biotransformation of bergenin (**1**) with white rot fungus *Pleurotus ostreatus* to produce C–C coupled dimeric bergenin derivative **35** (structure shown in Fig. 2) [229]. The IC_{50}

value of the dimeric compound (2.13 mM/mL) was doubled than monomer bergenin (**1**) (1.07 mM/mL) in their *in vitro* antioxidant activity in DPPH assay.

7.7. Degradation

Bergenin (**1**) was degraded with *Erwinta herbicola*, a strain of soil bacteria isolated from the rhizosphere of *Bergenia crassifolia*, into 4-O-methylgallic acid [230]. Hattori et al. also reported degradation of bergenin (**1**) into 4-O-methylgallic acid by a mixture of human intestinal bacteria isolated from human feces [231].

8. Total synthesis

Some attentions in the synthesis of bergenin have been paid in the past due to its interesting biological activities. In 1958, Hay and Haynes have reported the first synthesis of bergenin (**1**) by employing the reaction of tetra-O-acetyl-α-D-glucopyranosyl bromide with methyl-4-O-methyl gallate in the presence of sodium methoxide [5]. Although it was a low yielding procedure, the authors could establish the structure of bergenin (**1**) through the laboratory synthesis. Thereafter for about four decades, not much work has been done on bergenin except some reports on its isolation from the plant sources. Some attempts to prepare bergenin (**1**) were not successful [232,233]. Bergenin has gained much attention from the beginning of 21st century, as its pharmacological properties were gradually explored.

In 1991, a ten step synthesis of 8,10-di-O-methylbergenin (**7**) has been reported by Schmidt and coworker in overall 5.2% yield starting from perbenzylated trifluoroacetyl glucose (**99**) (Fig. 14) [234]. In the presence of $BF_3.OEt_2$, the β-glucosyl trifluoroacetate (**99**) was coupled with 1,2,3-trimethoxybenzene affording 4-β-C-glucosylarene **100**. Removal of the benzyl groups from compound **100** by hydrogenolysis followed by O-methoxycarbonylation with methyl chloroformate produced compound **101**. Bromination of **101** gave the 1-bromo derivative **102**. Bromine/lithium exchange with butyl lithium generated the lithiated species **103** *in situ*, which was reacted with diphenyl disulphide to yield the phenyl sulphide **104**. Oxidation of **104** with 3-chloroperoxy benzoic acid gave the diastereomeric sulphoxide **105** in 1:2 ratio. After chromatographic separation, the major isomer was treated with lithium di-isopropylamide to generate the C-lithiated compound **106**, which was reacted with methyl chloroformate to give compound **107**. Raney nickel desulphurization then produced the prebergenin-type compound **108**, which after lactonization by treating with methanolic sodium methoxide produced 8,10-di-O-methylbergenin (**7**). Acetalization of alcohol functionality with acetic anhydride in pyridine afforded compound **109**.

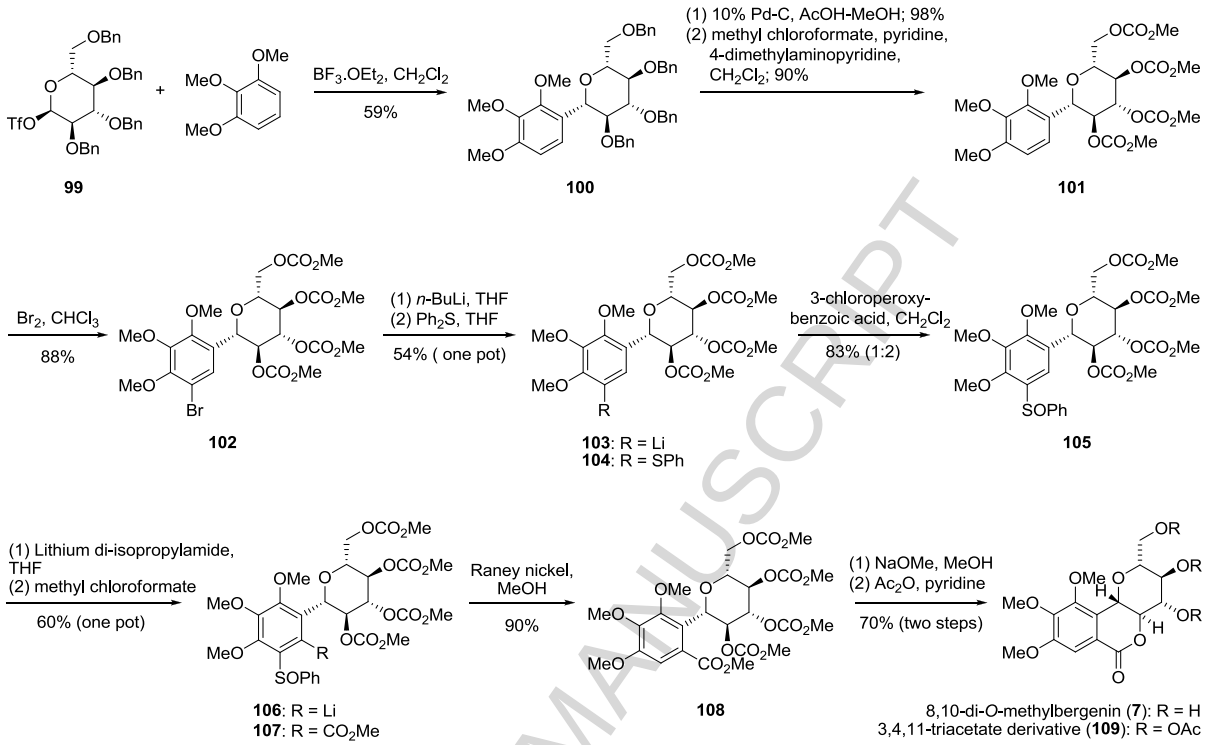


Fig. 14. Synthesis of 8,10-di-O-methylbergenin (**7**) [234].

Synthesis of peracetate of 8,10-di-O-methylbergenin (**109**) was reported by Martin and coworker, based on an intramolecular C-glycosylation of a 2-(3',4',5'-trimethoxy)benzyl n-pentenyl glucoside followed by oxidation of the benzylic methylene group (Fig. 15) [235]. Starting from peracetylated glucosyl bromide **110**, the compound **109** was obtained in 8.5% yield over nine steps. Tetra-O-acetyl-α-D-glucopyranosyl bromide (**110**) under Lemieux-Morgan conditions provided O-pentenyl orthoester (**111**). The acetyl groups in compound **111** were replaced with benzyl groups and treated with trimethylsilyl triflate followed by a base treatment afforded pentenyl β-glucoside **112**. O-Benzylation of **112** using 3,4,5-trimethoxybenzyl chloride provided compound **113**. The treatment of **113** with iodonium dicollidine perchlorate (IDCP) promoted intramolecular C-arylation affording **114**. The treatment of **114** with $BF_3.Et_2O$ resulted epimerization. The resulting product **115** was deprotected by hydrogenolysis and reacetylated. The benzylic position of **116** was oxidized using catalytic amount of ruthenium tetroxide to give the final lactone **109**.

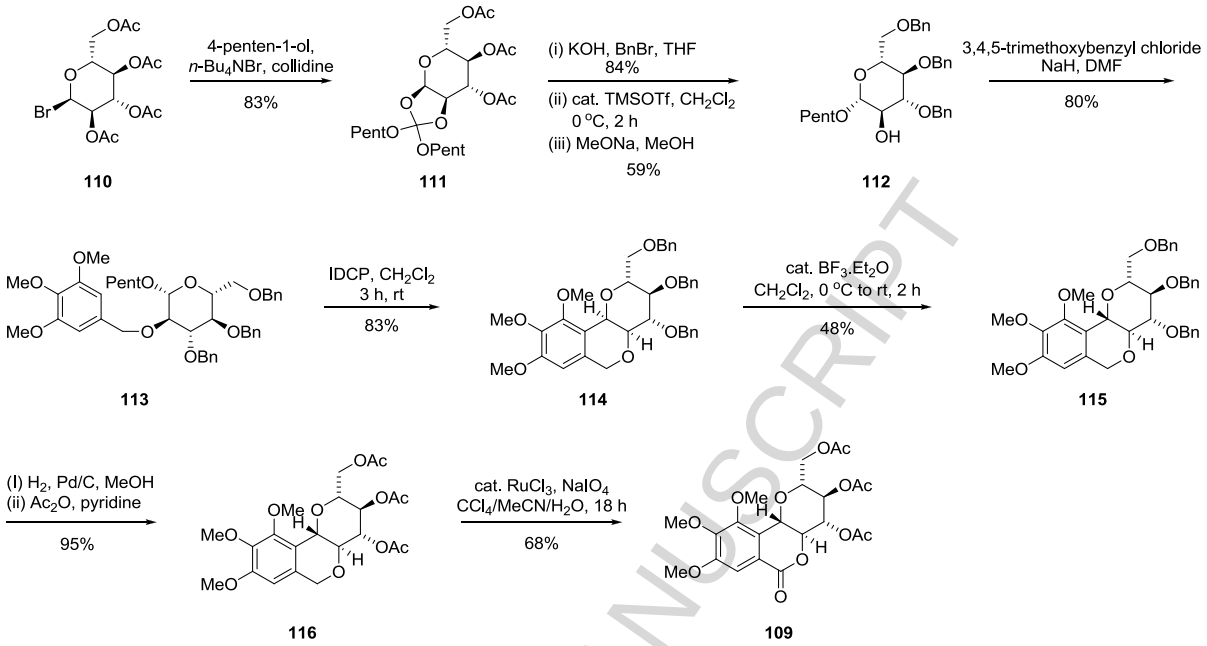


Fig. 15. Synthesis of peracetate of 8,10-di-O-methylbergenin (**109**) [235].

A short, five step synthesis of 8,10-di-O-methylbergenin (**7**) was reported by Seeberger and coworkers (Fig. 16) [236]. In the presence of trimethylsilyl trifluoromethane sulphonate (TMSOTf), 2,3,4,6-tetra-O-benzyl glucopyranosyl trichloroacetimidate (**117**) and perbenzylated glucosyl diphenyl phosphate **118** reacted with 3,4,5-trimethoxy phenol to produce the β-configured C-glycoside **119**. Triflate **120**, which was obtained upon treatment with triflic anhydride/lutidine, was subjected to Pd(0)-catalyzed aryl carbonation affording C-glucosyl benzoic acid derivative **121**. Hydrogenation of **121** with Pearlman's catalyst afforded debenzylated product. Finally, 8,10-di-O-methylbergenin (**7**) was obtained upon treatement of the debenzylated product with $SOCl_2$ in methanol.

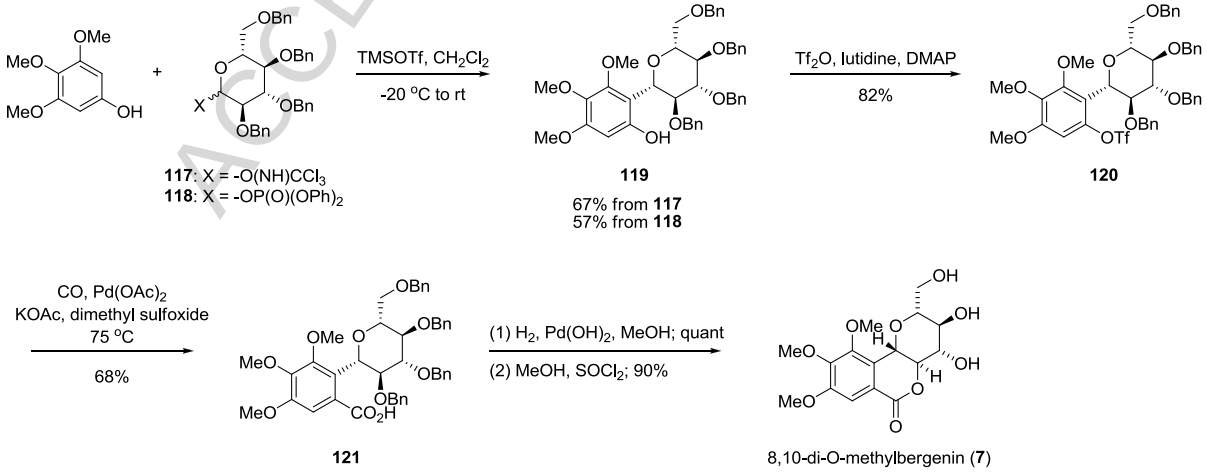


Fig. 16. Synthesis of 8,10-di-O-methylbergenin (**7**) [236].

Sakamaki and coworkers have synthesized 8,10-di-O-methylbergenin (**7**) by application of the aryl-β-C-glucosidation method (Fig. 17) [237]. Aryl bromide **123**, obtained by bromination of commercial methyl 3,4,5-trimethoxybenzoate (**122**), underwent Pd-catalyzed coupling reaction with glucal boronate (**124**). After hydroboration-oxidation, aryl-β-C-glucoside **126** was obtained. Compound **126** was oxidized with MnO_2 to produce lactone **127**. Deprotection of the silyl function afforded lactone-

ring opening product, which was cyclized in the presence of thionyl chloride to yield 8,10-di-O-methylbergenin (**7**).

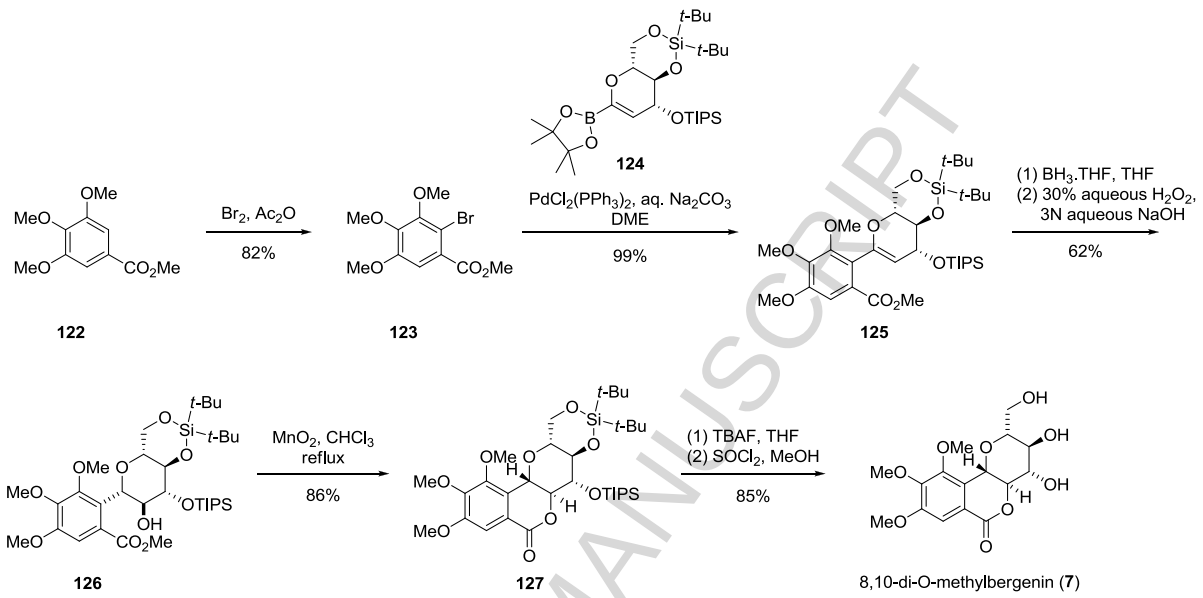


Fig. 17. Synthesis of 8,10-di-O-methylbergenin (**7**) [237].

While preparing this manuscript, the first total synthesis of bergenin (**1**) was reported by Parkan and coworkers (Fig. 18) [238]. Hydroboration-oxidation of the Suzuki-Miyaura cross-coupling product **129** furnished arylglucoside **130** diastereoselectively. Selective oxidation of the benzyl alcohol moiety was accompanied by cyclization to produce lactone **132**. Removal of silyl protecting group followed by reductive debenzylation afforded bergenin (**1**). Thus bergenin was synthesized in six steps from bromide **128** in 40% overall yield.

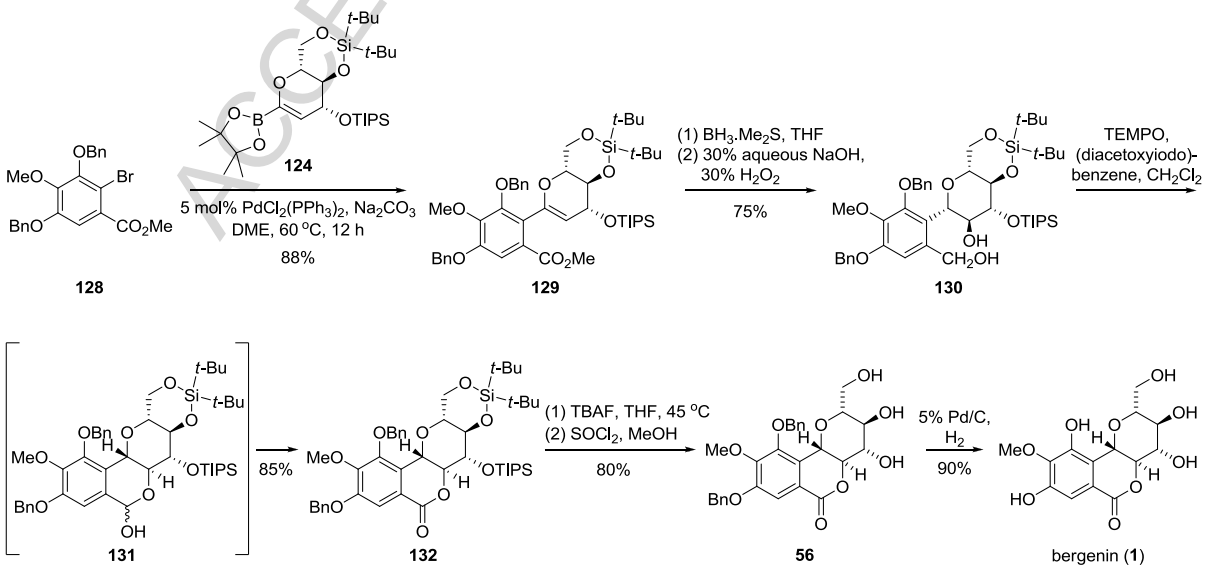


Fig. 18. Synthesis of bergenin (**1**) [238].

9. Conclusion

About 25% of medicines prescribed worldwide today are derived from plants and about 80% of the people living in the developing countries still rely on traditional plant-derived medicines [239]. Among the plant-derived medicines, bergenin (**1**) is considered as an antitussive agent. Literature

review reveals that bergenin exhibits antiviral, antifungal, antitussive, antiplasmodial, antiinflammatory, antihepatotoxic, antiarrhythmic, antitumor, antiulcerogenic, antidiabetic and wound healing properties. It displayed poor antimicrobial and antioxidant activities. In Ayurvedic formulations, bergenin containing plants (particularly *Bergenia ligulata*) are used to dissolve urinary calculi and the traditional use of the plant materials was also supported by the experimental results [240,241]; however, bergenin itself exhibited less significant antiurolithiatic activity [193]. Therefore, efficient antiurolithiac constituents present in genus *Bergenia* are essential to be searched. It can be concluded that bergenin is an important secondary metabolite that responsible for multiple actions for the betterment of human health. Bergenin is abundantly distributed in genera Saxifragaceae, Euphorbiaceae, Myrsinaceae, Dipterocarpaceae and Fabaceae. Up to 9.77% of bergenin was estimated to be deposited in the rhizome of *Bergenia purpurascens* (Saxifragaceae) [200]. Several bergenin derivatives were isolated from plants, synthesized in laboratories and studied their biological activities. Among them, norbergenin (**2**) is a most important and potentially bioactive constituent. Although bergenin was first isolated from the rhizomes of *Saxifraga* (*Bergenia*) *siberica* in 1881 [11], its structure was confirmed only in 1958 [5-7]. Bergenin has gained importance in scientific community only in 21st century when its pharmacological properties were gradually explored. As a consequence, a number of pharmacokinetic studies, analyses, isolation techniques and total synthesis of bergenin and its derivatives were recently reported. In conclusion, this article provides a comprehensive review on bergenin and its derivatives comprising all the available literature from the beginning and may help in development of new drugs in the future.

Conflicts of interest

The author has no conflicts of interest to declare.

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Graphical Abstract

Diversity, pharmacology and synthesis of bergenin and its derivatives: Potential materials for therapeutic usages

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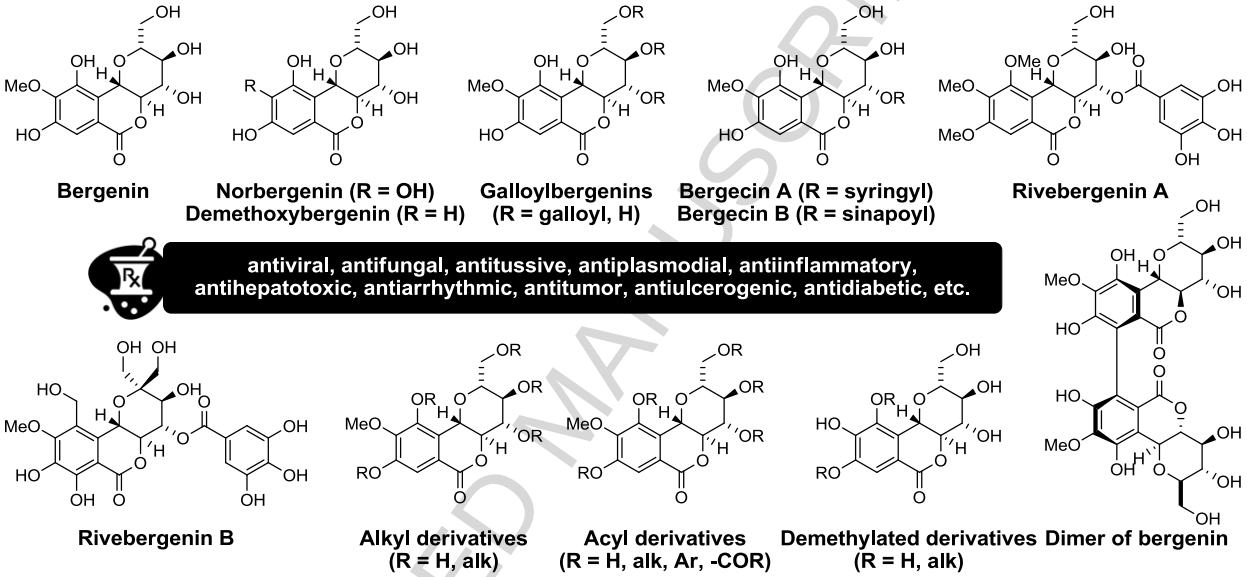

List of compounds discussed in the article and are entered in the NCBI PubChem Compound database:

Bergenin (PubChem CID: 66065)
Norbergenin (PubChem CID: 73192)
4-O-Galloylbergenin (PubChem CID: 14464332)
11-O-Galloylbergenin (PubChem CID: 14464334)
11-O-Syringylbergenin (PubChem CID: 195481)